PROTEIN METABOLISM AND BED SORES*

JOHN H. MULHOLLAND, M.D.,† CO TUI, M.D., A. M. WRIGHT, M.D., V. VINCI, M.D., AND B. SHAFIROFF, M.D.
NEW YORK, N. Y.

FROM THE LABORATORY OF EXPERIMENTAL SURGERY AND THE DEPARTMENT OF SURGERY, NEW YORK UNIVERSITY, COLLEGE OF MEDICINE; THE NEW YORK UNIVERSITY SURGICAL DIVISION OF BELLEVUE HOSPITAL, AND THE KING'S COUNTY HOSPITAL, BROOKLYN, N. Y.

THE SUBJECT OF DECUBITUS ULCERS or bed sores has received but cursory treatment in current textbooks on medicine and surgery. Present-day standard medical texts such as Cecil's,[1] and Christian's revisions of Osler,[2] merely refer to the occurrence of bed sores in some diseases of the central nervous system and in such debilitating diseases as typhoid fever and diabetes. Homan's[3] textbook of Surgery mentions debilitating diseases and poor nutrition of the skin as contributing causes in addition to local pressure. Cole and Elman[4] state: "Any poorly nourished patient suffering from prolonged and debilitating illness, as typhoid fever, tuberculosis, *etc.*, may develop bed sores unless adequate nursing care is exercised in turning the patient and protecting bony prominences."

Freeman,[5] writing in Keen's "Surgery: Its Principal and Practice" in 1919, under the chapter on mortification or gangrene, gave the subject a fairly extensive treatment. A comprehensive list of the usual sites was given; and the sores were divided into ordinary and decubitus accompanying lesions of the central nervous system. The etiology of ordinary bed sores was attributed to probable thrombosis of the smaller veins of the region, giving rise to gangrene, sloughing and ulceration. Other factors mentioned as more or less important were: (1) Hypostasis; (2) lack of tissue resistance caused by disease, weakness and defective metabolism; (3) alteration in vascular intima due to bacterial poisons, lack of nutrition from capillary stasis, changes in blood, *etc.*; and (4) evaporation of fluids from the tissues. It was also implied that local pressure injury was usually the immediate etiologic factor. Thus, there has not been much new added to the knowledge in the etiology of bed sores from 1919 to date. Exception, however, must be made of Joseph[6] who, in 1930, used insulin to improve the "general condition of the patient," and of McCormick,[7] who, in 1942, postulated that bed sores were caused by avitaminosis B.

Throughout this brief survey of the literature there runs the implication that malnutrition somewhat contributes to the development of bed sores. The therapy, however, except for McCormick's use of vitamin B, seems to make no provision for the improvement of nutrition. The principal measures may be briefly reviewed:

* Under a grant from Frederick Stearns & Company, Detroit, Michigan.

† Now Lt. Col. U. S. M. C.

Submitted for publication May 19, 1943.

1. Relief of local pressure:
   - Air mattresses
   - Rubber rings
   - Frequent turning
   - Sawdust beds[7]
2. Local stimulation:
   - Light massage
   - Sunlight
   - Infra-red radiation
   - Ultraviolet light radiation
3. Stimulation of healing with dressings of:
   - Balsam of peru
   - Cod liver oil
   - Gentian violet
   - Tincture of benzoin
4. Antiseptics
   - Chlorine and other compounds
   - Sulfonamides

Our interest in this condition was aroused by a case of extensive third degree burns who was losing so much protein from the burned areas that during the second week of his stay in the hospital, in spite of repeated plasma and blood transfusions, his total plasma proteins were 5.4 Gm.%. At this point he developed a bed sore over the sacrum. This occurrence suggested a possible relationship between hypoproteinemia and the development of bed sores. Accordingly, total plasma protein determinations were taken in 35 random cases of bed sores. The results with correlative data are given in Table I.

TABLE I

PLASMA PROTEIN CONCENTRATION, AND OTHER CORRELATIVE DATA, IN 35 CASES OF BED SORES

Ages Ranged from 30 to 81 Years; Nutritional States from Poor to Emaciated

T. P. Ranges Gm. %	No. of Cases	Ranges of Hematocrit Values	Description of Bed Sores
Above 6.40	0		
6.0 —6.35	6	42—44	All *, sim. (4 Psych., 2 Frac.)
5.5 —6.00	12	39—42	5*, 7**, 8 sim., 4 mult. (9 Frac., 3 Psych.)
5.0 —5.5	12	20—42	4*, 8***, 5 sim., 7 mult. (2 Pysch., 4 Frac., 6 Gen.)
4.0 —5.0	3	20—39.5	1**, 2****; all mult. (1 Frac.,2 Gen.)
3.75—3.8	2	15—22	1**, 1****; both mult. (both in Gen. Wd.)

* = Under 1 cm. in diameter
** = From 2 to 5 cm. in diameter
*** = From 5 to 10 cm. in diameter
**** = Over 10 cm. in diameter

Key
Psych. = Psychiatric Ward
Frac. = Fracture Ward
Gen. = General Ward
Sim. = Simple
Mult. = Multiple

It will be seen from Table I that all the cases had poor nutritional states, and that none of these 35 cases had a plasma protein concentration over

6.35 Gm.%. Six cases had plasma protein concentration of between 6.0 and 6.35 Gm.%, a range which may be called the upper limit of abnormal; and the other 29 cases were below 6.0 Gm.%. If the severity of the sores is now analyzed against the level of plasma proteins it will be seen that the extent and depth of the ulcers as well as the multiplicity seem to be related to the level of plasma proteins. It is also interesting that in the group of six with plasma protein ranges between 6.0 and 6.35, four were in the psychiatric ward and two in the fracture ward; and of the 12 in the plasma protein range of between 5.5 to 6.0, nine were in the fracture ward and three in the psychiatric ward, while none of the 18 in these two groups belongs to the general wards; and that all the cases from the general wards occurred in the groups below the plasma protein ranges of 5.5 Gm.%. The significance of this distribution will be commented upon later.

From the study of this table alone there seems to be a strong probability of a relationship between bed sores and hypoproteinemia.

One of the patients (p.p. 6.15 Gm.%) in the first group and one in the third group (p.p. 5.76 Gm.%) were placed on a high protein diet. The healing of the ulcer and the improvement in general condition were so prompt and definite that it was decided to undertake a controlled study of the nitrogen balance of a series of patients with bed sores, first under the usual ward feeding and then after they were placed on adequate caloric and nitrogen diet. Eight cases were embraced in this study.

EXPERIMENTAL CONSIDERATIONS

Nutritional Regimens.—Two of the eight patients for the first six days of study were placed on high caloric but low nitrogen diet. Table II is the protocol of one of these patients. The other six had a control period of the first three days during which the usual ward diets were given. The caloric and nitrogen figures were taken by subtracting the approximate values of food unconsumed from the values given for the diet as it appeared in the dietitian's charts. After these control periods the patients were given an amino-acid dextrose mixture* of homogenous composition dissolved in 500 cc. physiologic saline solution and enough water to make the mixture easy to administer. The patients were thus taking approximately 4.5 Gm. of NaCl daily. The water intake was unrestricted. When appetite returned, it was sometimes necessary to supplement the mixture with an egg sandwich, the caloric and nitrogen values of which were also calculated from the dietitian's charts. Tables III and IV are protocols representative of this group of six. During the entire hospitalization period all these eight patients had been receiving daily, by intramuscular injection, for a period of from 4 to 12 weeks, thamine chloride 30 mg.; nicotinic acid, 50 mg.; and cevitamic acid, 100 mg.

* This mixture was kindly prepared for our use by Frederick Stearns & Company, Detroit, Michigan.

Collection and Care of Laboratory Samples.—The urine was preserved with thymol, kept in the refrigerator, and pooled over each 72 hours. The urinary output ranged from 850 to 1250 cc. The feces of each patient were collected in two pooled specimens: one for the control and the other for the feeding periods. They were kept in sulfuric acid.

The hematocrit was usually determined each time the total plasma protein concentration was determined by the Barbour-Hamilton[8] method. When it was desired to determine albumin and globulin figures, the method of Wu and Ling, as modified by Greenberg,[9] was used. In determining the nitrogen of the urine and stools, the method of Rappaport, as modified by Levy and Palmer,[10] was used.

Weights of the Patients.—All the eight patients except one (D. P., Table II) were weighed periodically during the period they were under study. Bedridden patients were placed on a tared stretcher and the loaded stretcher was then weighed on two Howe platform scales, the two front wheels resting on the platform of one scale and the two hind wheels on that of the second. From the combined weight of the stretcher and patient was subtracted the weight of the stretcher, leaving the patient's weight. The sensitivity of each scale was 25 Gm., so that the sensitivity of the two-scale system was approximately 50 Gm.

Two of the cases had copious discharges, one from the bed sore itself (B. M., Table III), and the other from an unhealed amputation stump (Figure 4). The 24-hour discharges were collected on filter papers of predetermined weight and nitrogen content and then analyzed for total nitrogen, using the same chemical method as in the urine and stool determination. This source of nitrogen loss was also included in the figures for total nitrogen output.

EXPERIMENTAL RESULTS

The general results of the eight cases are so strikingly uniform that only three protocols need be given, each illustrating a point under investigation.

Table II (J. R.) embodies the findings of a case of simple and mild bed sores complicating fractures. He was one of the two cases who, during the first six days, were put on a high caloric but low nitrogen diet. He registered throughout these six days a negative nitrogen balance, a loss of weight, a slight depression in the plasma protein concentration, and no improvement in the ulcers. On the seventh day both of these patients were placed on a high caloric and high amino-acids diet with a resulting positive nitrogen retention. A gain in weight, an upswing in the plasma protein concentration took place, and healing became perceptible on the fourth day after the high protein diet was started. The hematocrit values remained relatively unchanged throughout the course of the work.

Table III represents the nitrogen balance studies of D. P. who, as a result of impaired appetite and diarrhea, following an operation for repair of a traumatic rupture of the sigmoid, was in a poor nutritional state. The

TABLE II

J. R., MALE, AGE 56, ADMITTED 7-13-42; FRACTURE UPPER RIGHT FEMUR; BED SORE 5 WEEKS, SLOWLY ENLARGING

Date Sept.	Caloric Intake	N. Intake Gm.	N. Output Gm.	N. Balance Gm.	Hemato-crit	P. P. Gm. %	P. Alb. Gm. %	Wt. Lbs.	Description of Bed Sores
6–7					41	6.2	3.3	102.5	Over sacrum; 1 cm.; sluggish, greyish base; involves subcutanous tissue.
7–8 8–9 9–10	9300	18	22.6	—3.3					
10–11 11–12 12–13	9300	18	21.25	—3.25	40.5	5.9		99.25	No improvement.
13–14 14–15 15–16	8420	48.6	31.42	16.58				102	Base pink; granulations forming.
16–17 17–18 18–19	9165	52.45	31.74	20.71	395	6.2		106.5	
19–20 20–21	9165	52.45	35.3	15.15	40	6.6		110	0.5 cm. in diameter.
21–30	3800 daily	25 daily			41	6.9	4.1	115	Healed on 9/30.

presence of edema consequent to a total plasma protein concentration of 4.6 Gm.% made it useless to follow the weight curve. During the first three days (*i.e.*, October 7–10) the patient's caloric and nitrogen intakes were calculated from the portions of the prescribed diets which he consumed. He lost 1.02 Gm. of nitrogen during these three days. During the subsequent nine days he was given the amino-acid-carbohydrate mixture described above, with the result that he was on a positive balance daily. Signs of healing were definite on the fourth day, and the ulcer, which was initially superficial, was healed on the ninth day. It will be noted that the hematocrit did not change materially during these days, the slight fall being perhaps due to increased blood volume as a result of a higher plasma protein concentration.

TABLE III

D. P., MALE; AGE 61, ADMITTED INTO KING'S COUNTY HOSPITAL 8-9-42, WITH DIAGNOSIS OF TRAUMATIC RUPTURE OF RECTOSIGMOID. OPERATION FOR CLOSURE OF PERFORATION. BED SORES BEGAN 9-10-42.

Date Oct.	Caloric Intake	N. Intake Gms.	N. Output Gm.	N, Balance	Hemato-crit	P. P. Gm. %	P. Alb. Gm. %	Description of Bed Sores
7–8 8–9 9–10	3386	22.4	33.42	—11.02	22	4.6	2.8	Sacral; 4 cm. involves dermis. No signs of healing; edema of ankles.
10–11 11–12 12–13	9300	64:8	42.94	+21.86				
13–14 14–15 15–16	9300	64:80	35:04	+29.76	20	5.3		Base healthier; granulations forming.
16–17 17–18 18–19	9300	68:80	41:2	+27.8	19	5.9		Ulcer almost healed.

Table IV represents a patient (B. M.) whose bed sore was exceedingly severe, in area as well as in depth. The pictures in Figure 1 represent different stages of healing. As in the other cases, signs of healing were definite on the fourth day after the nitrogen balance was reversed from negative to positive. The plasma proteins and the body weight both underwent a corresponding rise. The original ulcer was so extensive that the first day's discharge contained 893 mg. of nitrogen, corresponding to the loss of almost 5.56 Gm. of protein, or 113 cc. of plasma of the protein concentration of that day.

TABLE IV

B. M., MALE, AGE 41; ARTERIOSCLEROTIC GANGRENE OF RIGHT FOOT. AMPUTATION AT KING'S COUNTY HOSPITAL 6-11-42. BED SORES BEGAN 8-15-42.

Date Oct.	Caloric Intake	N. Intake Gm.	N. Output Gm.	N. Balance Gm.	Hemato-crit	P. P. Gm. %	P. Alb. Gm. %	Wt. Lbs.	Remarks Description of Bed Sore
7–8									
8–9	2700	16.8	32.375	—16.375	34	4.9	2.2	94	9″ x 6″ x 1″. Dirty, greyish, sloughing base; necrotic edges.
9–10									
10–11									
11–12	9300	64.8	42.73	+22.068					
12–13									
13–14									
14–15	9300	74.9	35.761	+39.139					Base cleaner; granulations forming.
15–16									
16–17									
17–18	9300	78.9	36.8298	+42.07				995	
18–19									
19–20					36	5.42	2.7		
20–21	9300	78.9	44.826	+34.072					
21–22									
22–23									
23–24	9300	78.9	37.8	+41.1				104	
24–25					36	5.58	2.96		Healing rapid. 7″x5″x¾″
25–26									
26–27	9300	78.9	51.166	+20.73					
27–28									
28–29									
29–30	9300	78.9	42.276	+33.624					
30–31					36	5.82	3:2	115.5	5″ x 4″ x ½″

In Figure 1 are photographs of different stages of healing of this patient. The wound healed rapidly at first but lost momentum, and it took almost three months to effect a complete healing of this ulcer which was initially 9 x 7 x 2 inches.

Figures 2 and 3 show the stages in the healing of two other patients whose protocols are not shown here but whose healing followed the usual pattern of being visibly definite three or four days after the nitrogen balance was reversed from negative to positive. Figure 3 also shows an amputation stump which evinced no healing when the bed sore developed, but which began healing as soon as the bed sore showed signs of healing.

COMMENT AND DISCUSSION

This study may be said to have gone through three stages. The suggestion given by the development of bed sores in a case of burns, with

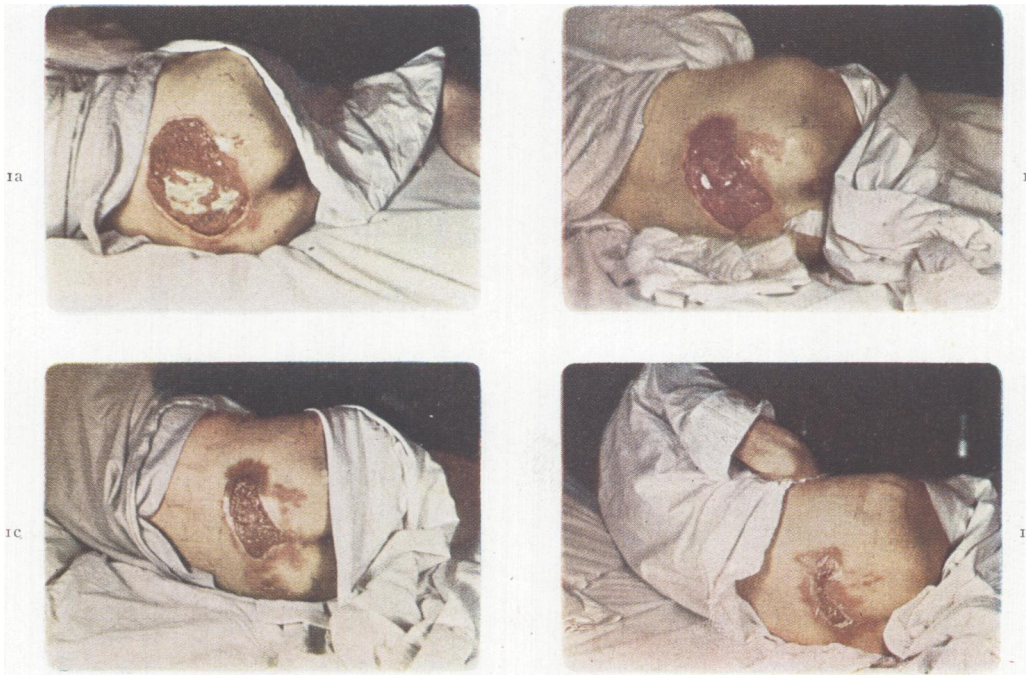

FIG. 1.—Panel 1a shows the ulcer of patient B.M., Table IV, in the original state. Note the greyish, necrotic base and edematous granulations. Panel 1b shows the ulcer one week after nitrogen balance was reversed from negative to positive, and maintained. Note the healthier color. Panels 1c and 1d show the ulcer during, respectively, the 6th and 12th weeks.

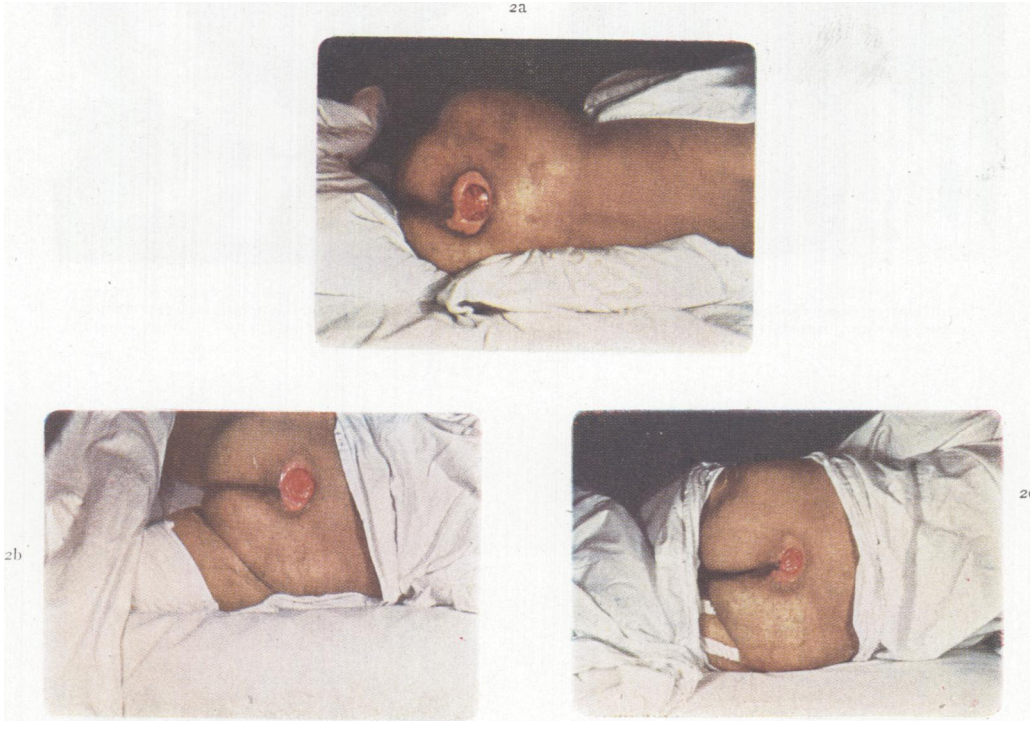

FIG. 2.—Panel 2a shows the original bed sore, undermined, livid, and glistening with edematous granulations, and with no tendency to heal. Panels 2b and 2c show the state of the ulcer three and six weeks after maintenance of nitrogen balance. Note the pink, healthy granulations in both panels.

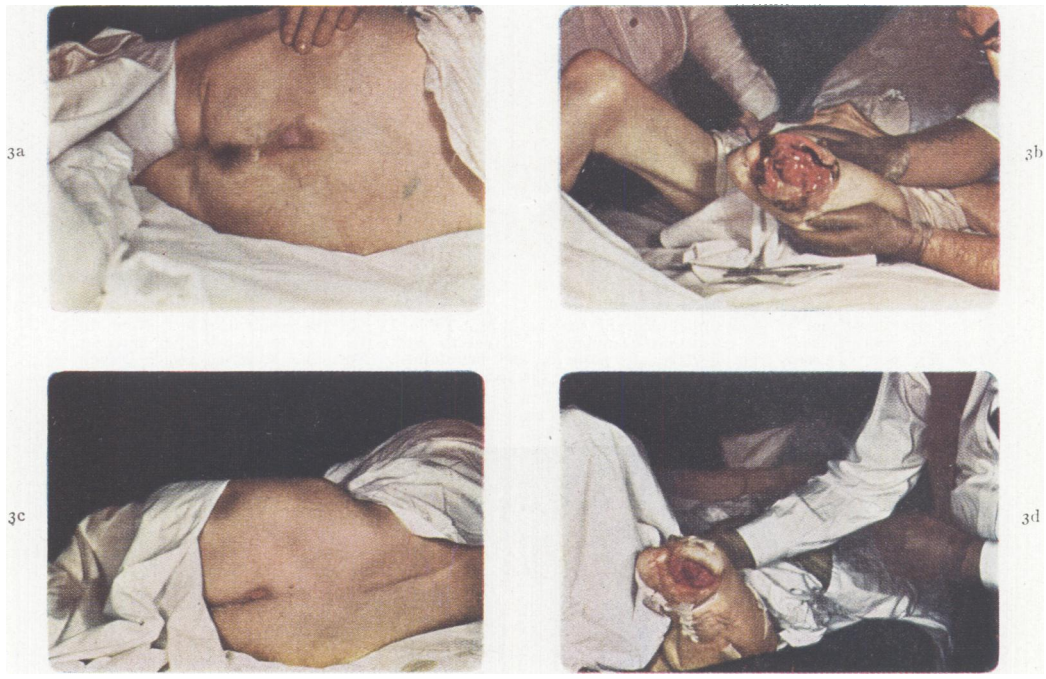

FIG. 3.—Panels 3a and 3b show, respectively, the original sore and the unhealed amputation stump. In the latter, note the necrotic edges, the greyish exudate, and the livid and glistening tissue. Panels 3c and 3d show, respectively, the healed ulcer 12 days after treatment, and the healing amputation wound.

hypoproteinemia, became a probability when the plasma protein concentrations of a series of 35 cases were determined and correlated with the severity of the ulcers, and when a high protein diet was found to cause healing in the only two of these 35 in whom high protein diet was instituted. The probability was confirmed by the controlled nitrogen balance studies of eight patients with bed sores.

The failure of the ulcer to heal with high caloric and low nitrogen diet for six days in two cases, as represented by J. R. (Table II), and the occurrence of signs of healing on the fourth day after the nitrogen balance was made positive, showed that it was not high caloric intake which initiated the healing. The use of a mixture which contained no fat indicated that fatty acids are not essential in the healing of these sores, which was implicated. The narrow ranges in which the hematocrit changed during the study period, and the fact that D. P. (Table II) had a hematocrit of only 22 throughout the healing period, indicated the lack of direct relationship between anemia and the development of bed sores. The vitamin therapy to which these patients were subjected through their hospital stay, prior even to the development of bed sores, indicated that, in the presence of hypoproteinemia, vitamins do not prevent the development of bed sores. Finally, the prompt healing becoming evident four days after protein anabolism was achieved points to a definite relationship between protein metabolism and the development of decubitus ulcers.

At this point, it may be pertinent to state the rôle of protein nutrition in the causation of bed sores. It is known that a certain amount of pressure applied locally to even a normal tissue for a sufficient length of time can cause necrosis of that tissue. In patients with protein malnutrition the tissues are so changed in character that it apparently takes a smaller amount of pressure, or the same amount of pressure for a shorter length of time, to cause tissue necrosis. It may also be expected that when the malnutrition reaches a certain point even the amount of pressure exerted by the recumbent body for the usual period of rest may cause tissue necrosis.

This combination of pressure and of tissue of "a changed character" in the causation of bed sores explains the distribution of the 35 cases in Table I in the fracture, the psychiatric and the general wards. In the psychiatric ward all the patients had large doses of hypnotics, which constrained the patients to lie unconscious in one position for a long time. In the fracture cases this same constraint was exerted by a plaster encasement. Meanwhile the loss of nitrogen from the body, either as a result of "toxic loss" due to the injury, or as a result of undernutrition, or of the combination of both, alter the character of the tissues. In the general ward, however, the patients were able to change positions more freely and thus would not develop sores until malnutrition was more marked.

This same hypothesis of combined causation would also explain the

fact observed by Cushing[11] that marasmic infants develop bed sores on the back of the scalp, since in the infant the head is perhaps the heaviest part of the body.

Abbott and Mellors' observations[16] that a patient with several decubiti healed rapidly after anabolism was achieved by sufficient caloric and protein intake and that several similar patients also healed rapidly when given repeated plasma transfusions are consonant with this hypothesis.

Apart from the light which this study throws on bed sores, the implication that tissues of patients with poor protein nutrition have this character of impaired viability is significant in connection with the entire problem of protein nutrition. It has previously been shown that tissues of hypoproteinemic individuals have impaired healing powers,[12, 13, 14] and Altshuler, *et al.*[15] have recently shown that intractable surface ulcers heal in response to amino-acid therapy.

Whether the same causative factors are also operative in bed sores occurring in cases of transverse myelitis, and other diseases of the central nervous system, remains for further study. The favorable response obtained by McCormick in his one case to improved nutrition suggests a similar etiologic factor.

SUMMARY AND CONCLUSIONS

1. In 35 random cases of bed sores, it was found that the plasma protein concentration were invariably below the lower limits of normal.

2. In a controlled study of two other cases it was found that the giving of a high caloric diet resulted in further weight loss to the patient, in a negative nitrogen balance throughout the six days, in a depression of the plasma protein concentration, and in no improvement in the condition of the sores.

3. In six other cases it was found, during a control period of three days, that the diets they were taking in the wards resulted in a negative nitrogen balance, a slight loss of weight, and lack of improvement of the ulcers.

4. In all the eight cases there was improvement in the general condition, gain in body weight (except D. P. in whom the weight was not followed), a rise in plasma proteins, and healing of the ulcer when the nitrogen balance was reversed from negative to positive.

5. Fatty acids are not essential to the healing of bed sores; and in the presence of protein deficiency vitamins do not seem to prevent the development of bed sores.

6. The theory is advanced that both local pressure and a tissue of impaired vitality as a result of protein deficiency are factors in the causation of bed sores.

Grateful acknowledgment is made to Dr. Irving Barcham and to the Hospital for Joint Diseases, New York, for contributing two of these cases.

REFERENCES

1 Cecil, R. L.: Textbook of Medicine, ed. 5, Philadelphia, W. B. Saunders, 1940.
2 Christian, H. A.: Osler's Principles and Practice of Medicine, ed. 14, New York, Appleton-Century, 1942.
3 Homans, J.: A Textbook of Surgery, ed. 5, Springfield, Illinois, Charles C. Thomas, 1940.
4 Cole, W. H., and Elman, R.: Textbook of General Surgery, ed. 5, New York, Appleton-Century, 1941.
5 Freeman, L.: Chapter, Ulceration and Ulcers, Keen's Surgery: Its Principle and Practice, vol. 1, Philadelphia, W. B. Saunders, 1919.
6 Joseph, B.: Insulin in the Treatment of Non-Diabetic Bed Sores. ANNALS OF SURGERY, **92,** 318, 1930.
7 McCormick, W. J.: The Nutritional Aspects of Bed Sores. M. Rec. **154,** 389, 1941.
8 Barbour, H. G., and Hamilton, W. F.: The Falling Drop Method for Determining Specific Gravity. J. Biol. Chem., **69,** 625, 1926.
9 Greenberg, D. M.: The Colorimetric Determination of the Serum Proteins. J. Biol. Chem., **82,** 545, 1929.
10 Levy, M., and Palmer, A. H.: Iodometric Estimation of Small Quantities of Nitrogen with Distillation. J. Biol. Chem., **136,** 57, 1940.
11 Cushing, H.: Chapter, Surgery of the Head, Keen's Surgery: Its Principle and Practice, vol. 3, Philadelphia, W. B. Saunders, 1919.
12 Thompson, W. B., Ravdin, I. S., and Frank, I. L.: Effect of Hypoproteinemia on Wound Disruption. Arch. Surg., **36,** 500, 1938.
13 Koster, A., and Shapiro, A.: Serum Proteins and Wound Healing. Arch. Surg., **41,** 723, 1940.
14 Hartzell, J., Winfield, J. S., and Irvin, J. L.: Plasma Vitamin C and Serum Protein Levels in Wound Disruption. J. A. M. A., **116,** 669, 1941.
15 Altshuler, S. S., Sahyun, M., Schneider, H., and Satriano, D.: Clinical Use of Amino-Acids for the Maintenance of Nitrogen Equilibrium. J. A. M. A., **121,** 163, 1943.
16 Abbott, W. L. and Mellors, R. C.: Total Circulating Plasma Proteins in Surgical Patients with Dehydration and Malnutrition. Arch. Surg., **46,** 277, 1943.